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DRAWINGS ATTACHED

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(54) IMPROVEMENTS IN OR RELATING TO AEROSOL SPRAY COMPOSITIONS

(71) We, MINNESOTA MINING AND MANUFACTURING COMPANY, of 2501, Hudson Road, Saint Paul, Minnesota, United States of America, a corporation organised and existing under the laws of the State of Delaware, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

From the early history of surgery, the suture closure method has been considered the fundamental technique of surgical tissue closure, and generally ligation and electrical cauterization have served as fundamental methods of surgical hemostasis. The disadvantages inherent in these methods have given rise to the development of new approaches to the joining together of damaged mammalian tissues, as well as for arresting the escape of blood through such tissues. Accordingly, there has recently appeared in the art an adhesive and hemostatic agent consisting essentially of monomeric α-cyanoacrylate esters which when polymerized in place on tissue appears to have the desired physiological properties, viz., tolerance by the tissues, good adhesion and low toxicity, and possibly biodegradability.

Attempts to employ this biological tissue adhesive to full advantage have been hampered by serious problems in connection with methods of application. Chief among these problems have been difficulties in controlling the amount of adhesive-forming monomer dispensed and the pressure or force with which it is delivered and in eliminating the tendency of the monomer to polymerize within the dispensing apparatus. Another problem has been to keep the applicator at minimal size and simplicity.

Heretofore the art has been unable to provide a satisfactory one-part application system for biological tissue adhesives. Thus, so far as is known, monomers for producing such adhesives have not been packaged in a single container containing the monomer in solution in a propellant, nor has the use of an inert material for the inhibition of premature or undesired polymerization within the dispensing system been suggested.

While the heretofore used methods of applying biological adhesives may be effective in certain controlled laboratory experiments, their relatively complicated modes of operation, e.g. coordination of separate propellant and adhesive containers, utilisation of air brushes with bulky hoses, etc. are not easily adaptable to the rigid demands of the operating room. In emergency situations where damaged tissues require immediate and rapid closure or hemostasis, if a biological adhesive is to be employed, it must be applied in controlled amounts, to specific areas, with the appropriate force or pressure to preclude further damage to the tissues; further, the applicator should be compact, portable, adaptable and reliable.

This invention relates to improvements in the packaging and dispensing of monomeric materials which polymerize rapidly on contact with e.g. moisture or air, to form adhesives. Included within the scope of the invention are improvements in controlling the concentration and quantities of monomer dispensed, in the ability to reduce clogging within the system due to premature polymerization, and in the ability to localize the dispensed material and to direct it toward confined areas. Further, the physical size and simplicity of the spray apparatus employed results in improved adaptability and convenience of the system. This package and spray system is especially adapted for use with biological adhesives as will be explained in more detail hereinafter.

The present invention meets the demands of the medical arts by providing a convenient, compact, one-part system, adaptable for

surgical contingencies, wherein the monomer-propellant solution is packaged in a single container. It provides a method for applying biological adhesives to localized areas in controlled amounts by means of the valve and actuator system, Optionally provided with an extension tube extending outward from the discharge orifice.

According to this invention, a pressurized aerosol dispensing package for adhesives comprises a chemically inert, pressure-tight container having discharge passageways with a valve, a valve actuator and delivery means for controlling the escape of the contents of the container via a discharge orifice therefor, which contains an anhydrous adhesive-forming monomer dissolved in an anhydrous propellant compatible with the monomer, an inert lubricant for facilitating the escape of the contents of the container being provided within the discharge passageways so that a film of the inert lubricant is present upon the internal surfaces of the passageways of the valve, the valve actuator and the delivery means when the actuator has been operated.

In one embodiment of the dispensing package of the invention, the inert lubricant is located adjacent to and occludes the outlet of the valve and is of such density and kinematic viscosity that the vapour pressure of the anhydrous propellant, upon first being actuated, propels the inert lubricant through the passageways of the valve actuator and the delivery means and deposits the film of lubricant thereon.

In another embodiment, the inert lubricant is provided upon the passageways of the valve, the valve actuator and the delivery means prior to first use of the package.

Preferably, the discharge orifice is provided with means for localizing the spray discharge.

The physical size and simplicity of the dispensing package of this invention allow it to be used conveniently in many different situations. The plug or film of lubricant is effective to prevent premature, moisture-activated polymerization of the monomer and resultant clogging of the system. Further, the monomer-propellant system of the invention is well adapted for use in sterile procedures used in operating rooms.

The excellent results observed in hemostasis using the system of the invention may be due to the presence of small amounts of propellant at the treated surface, as the monomer is in solution when sprayed and not all of the solvent may be evaporated until after the monomer has contacted the surface. A more uniform coating may thus be formed.

Thus, the dispensing package of this invention makes possible the spray application of biological tissue adhesives by the utilization of a single aerosol-dispensing apparatus housing both the propellant and the adhesive monomer.

Further, the container of the invention for the spray application of tissue adhesives is free of clogging due to premature moisture-activated polymerization of the monomer and permits localization of the monomer and allows it to be directed toward confined areas.

A method of treating non-human mammalian body tissue and a sprayable adhesive composition therefor are disclosed and claimed in our co-pending Application No. 53296/69 (Specification No. 1,227,873).

In the embodiment of the invention shown in the accompanying drawing:

Figure 1 is a front elevational view of a container formed according to the present invention;

Figure 2 is a vertical sectional view of the container illustrated in Figure 1 showing the interior elements and the position of the inert coating material relative to the valve, actuator and extension tube prior to the first actuation of the aerosol valve container;

Figure 3 is an enlarged fragmentary vertical sectional view of the invention showing the valve, actuator and extension tube coated with inert material lubricant after the first actuation of the valve.

Referring to Figures 1—3, a container 10 is formed with a neck 11 forming an open end on the container and a ferrule 12 secured to the neck. The ferrule 12 covers the open end of the container and serves to support a finger-depressible valve actuator 13 and to secure a dip-tube assembly 14 over the open end. The valve actuator 13 has a passageway formed therein, the upper portion of which communicates with an external orifice 15 in which is fitted a hollow cylindrical extension tube 20. The lower end of the valve actuator extends downward through the ferrule 12 and contacts the valve member 21. The dip-tube assembly 14 comprises a cylindrical hollow tube 22, the lower end of which extends downward into a monomer-propellant solution 23 while its upper end is diametrically enlarged to form a chamber 24 to house the valve spring 25 and the valve member 21. The upper end of the chamber 24 widens into a flange 30, the edges of which contact the neck of the container, and has a gasket 31 on its under side and a second gasket 32 on its upper side in contact with the ferrule. The outer edges of the flange 30 and the gaskets 31 and 32 engage the neck of the container to form a seal therewith. Upon depression, the valve actuator 13 forces the valve member 21 downward against the action of the spring 25, causing the monomer-propellant solution 23 to escape through the passageway of the valve actuator 13 and out through the orifice 15 and the extension tube 20.

Prior to the initial actuation of the aerosol

apparatus, the area immediately surrounding the valve member 21 is filled with a quantity of an inert lubricant 33, e.g. a polymer wax, preferably poly(chlorotrifluoroethylene) of low molecular weight. This material is inert, i.e. does not react with, activate or cause polymerization of the monomer used, and has lubricant properties which inhibit adherence of the solution of monomer to the walls of the passages. The material also coats the walls of the passages to prevent contact of the monomer with any moisture which may have become adsorbed thereon during storage. Thus, premature initiation of polymerization is prevented. The material can be characterized as an inert lubricant, although it may be characterized as a coating material.

The physical properties of such a lubricant must be such that the vapour pressure of the propellant system will be capable of forcing it through the valve, actuator and extension tube. Critical criteria for the material are that it:

1. has a density between 1—2.5;
2. has a kinematic viscosity of 35—45 centistokes at room temperature, viz. 10°—25°C.; and
3. is highly stable.

The preferred lubricant is poly(chlorotrifluoroethylene); it has a density of 1.96 at a temperature range of 4° C. to 38° C. and a kinematic viscosity of 40 centistokes. Upon initial actuation of the apparatus, the polymer wax 33 is forced out through the valve actuator and extension tube, thus depositing on all of the internal surfaces a thin coating 24 of the polymer wax. The coating is effective to prevent clogging of the apparatus due to premature polymerization of the monomer within the system.

In another embodiment of the container, the waxy inert lubricant is applied to the inner surfaces of the valve and the passages through which the monomer-propellant solution passes, before the container is filled. Most usefully these passages are also sealed to prevent access of moisture to such areas prior to use, so there will not be any likelihood of undesirable polymerization within the said passages.

The chemical properties of the α-cyanoacrylates employed as biological tissue adhesives, most particularly their strong tendency to polymerize upon the slightest exposure to moisture (that in the atmosphere for example), require that the materials employed in the construction of the apparatus be compatible (i.e. unreactive) with the monomeric adhesive and that the entire system be impervious to moisture. The effect of any premature polymerization of monomer within the apparatus is to cause clogging of the valve, actuator and extension tube and thereby reduce the shelf life and operational reliability of the dispenser.

A container made of polyacetal resin is preferred. The acetal polymer has a highly crystalline nature, which imparts excellent resistance to solvents. It is compatible with α-cyanoacrylate monomers and is strong enough to withstand the internal pressures normally encountered with aerosol propellants. Premature polymerization ordinarily occurs when uncoated metal containers are used.

The preferred container is of one ounce capacity and has a wall thickness of 55 mils, although of course other sizes of containers can be employed. Other containers with similar inert nature can be used, e.g. metal containers suitably coated on the interior with a polymer- glass containers similarly coated, and the like.

Preferably the valve, actuator and dip-tube system is constructed of polyethylene and has a finger-depressible head modified to accept a cylindrical extension tube at the point of the actuator's discharge orifice. The extension tube is also constructed of inert polymeric material, preferably polypropylene, and its length may be modified to fit the specific requirements of the surgeon. The effect of the extension tube is to permit localization and direction of the spray toward confined areas.

The invention requires a propellant system which is compatible with the monomer, physiologically non-toxic and having vapour pressure sufficient for operating the aerosol but yet low enough so as not to cause physical damage to the tissues being treated through impact of the pressurized stream. A number of the propellants known as "Freons" (Regd. Trademark) can be used for the purpose. The preferred propellant system for the invention is a mixture of CCl_3F and CCl_2F_2 in the ratio of 40 parts CCl_3F to 60 parts CCl_2F_2. At 70° C. the 40/60 propellant system has a vapour pressure of 45 psi which provides a uniform spray, is sufficient to coat the valve, actuator and extension tube with lubricant, propels the monomer with sufficient speed so as to ensure rapid hemostasis or tissue closure, substantially prevents tissue damage, and allows safe and uncomplicated placement of the actuator on the aerosol bottle.

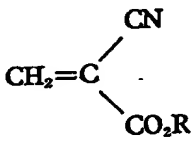
The ratio of propellant to monomer may vary according to the type of adhesion required. For example, in certain instances hemostasis may require a relatively small amount of monomer, whereas tissue closure would require a greater amount. We have observed that propellant to monomer ratios within the range of 10 to 1 up to 15 to 1 will satisfactorily meet adhesion requirements varying between minimal hemostasis and sealing massive effusion from capillaries or bleeding from larger vessels. Thus it has been observed that the 10 to 1 ratio provides a

uniform but somewhat thick coating of adhesive with good hemostasis, whereas the 15 to 1 ratio coating, although uniform and thin, occasionally requires a second application for hemostasis. When tissues are to be adhered, two or more coats may be required. Thus it is noted that both the propellant system and the propellant-monomer ratio can be modified to meet differential surgical requirements.

The aerosol may be loaded by injection or cold fill techniques, both conventional methods. The cold fill method is preferred, however, since it permits convenient and accurate control of the propellant: monomer ratio.

While the unique features of this invention provide improved methods for packaging and dispensing anhydrous biological tissue monomers and for tissue closure and hemostasis, the monomers employed are not limited to the biological adhesive-forming type. The inert lubricant coating of the valve member, actuator and extension tube of the aerosol will function to keep those members unobstructed when any rapidly polymerizable monomer is employed.

The monomers satisfactorily employed include monomeric α-cyanoacrylate esters of the formula



wherein R is alkyl, cyclohexyl, phenyl, 2(2,2,2 - trifluoroethoxy)ethyl, 1,1,1 - trifluoroisopropyl or CH_2R' wherein R' is a radical of the group consisting of phenyl, alkylthioalkylene, alkoxyalkylene and halogenated alkyl groups, said radical having from 1 to 7 carbon atoms.

Such monomers and methods for their preparation are described in U.S. Patents Nos. 2,721,858; 2,467,926; 2,763,677; 3,255,059 and 2,784,215. In many cases they polymerize very rapidly after initiation of polymerization by even traces of moisture, or even on being spread in a thin film, without heat or a catalyst. Accordingly, they are prepared in such manner that they are free from water which would initiate polymerization; and they may also contain small amounts of a polymerization inhibitor, e.g. sulfur dioxide, hydroquinone and the like.

When the invention is employed in the field of tissue sealing or hemostasis, the preferred monomers are 2,2,2-trifluoroethyl α-cyanoacrylate (i.e. the radical R' is CF_3), the corresponding pentafluoropropyl monomer (i.e. the radical R' is C_2F_5, namely perfluoroethyl) and 1,1,1-trifluoroisopropyl α-cyanoacrylate, these monomers being preferred because of their excellent physiological properties of low toxicity, good adhesion and compatibility with mammalian tissues. Another preferred monomer is 2(2,2,2-trifluoroethoxy)ethyl - α - cyanoacrylate. These monomeric materials polymerize very rapidly upon contact with the moisture in body tissues, even if a small amount of the propellant solvent is still present.

In order to illustrate the novel improvements of the invention and preferred embodiments thereof, the following examples are given.

Example 1

Hemostasis in Vascular Organs (Excised Rat Liver)

The livers of 10 ether-anesthetized white rats were exteriorized and the distal 1/4 to 1/3 of the left lateral lobe of each liver was excised. Hemorrhage at the open surface of the remaining lobe was preliminarily controlled by digital compression and sponging with gauze. Immediately after sponging, a thin layer of the adhesive-forming monomer was applied to the cut surface by means of the aerosol dispensing package of this invention. In each experiment, the monomer was applied by a momentary actuation of the aerosol apparatus, with the distal end of the extension tube being held at a distance of from 4 to 8 centimetres from the cut surface. After allowing sufficient time for polymerization of the monomer, the digital pressure was released, the liver was replaced into the peritoneal cavity, and the muscle and skin wounds were closed with conventional sutures. Adhesive and hemostatic properties were recorded at the time of application. Necropsies were performed on each of two animals, with examination of the livers, two, three, four, six and eight weeks, respectively, after surgery.

The lubricant used in the package, to occlude the valve chamber and coat the internal dispensing passages upon initial use, was poly(chlorotrifluoroethylene) grease, "Kel-F" No. 40 (Regd. Trademark).

The monomer employed was 2,2,2-trifluoroethyl α-cyanoacrylate, and the propellant system was a mixture of CCl_3F and CCl_2F_2 in 40:60 ratio. In five animals the propellant: monomer ratio of the solution was 10:1, whereas in the other five animals the propellant: monomer ratio of the solution was 12:1.

In each case, the monomer polymerized rapidly and provided rapid and complete hemostasis. Occasional point bleeding or seepage through the adhesive layer was controlled by a second application. All of the animals remained in good general health throughout the two to eight week testing period. In the five animals in which the monomer: propellant ratio was 12:1, it was observed that the adhesive layer was relatively thinner when

compared to the animals in which the ratio used was 10:1. However, in all ten animals, complete and satisfactory hemostasis was obtained.

Similarly useful results are obtained when 2(2,2,2-trifluoroethoxy)ethyl α-cyanoacrylate, methyl α-cyanoacrylate and 1,1,1-trifluoroisopropyl α-cyanoacrylate are the monomers employed.

Tests have shown the solution of adhesive-forming monomer in the propellant to be stable in the container for periods of about six weeks at room temperature or longer when frozen. Even when used intermittently during this period, the passages remained open so that the containers could be used repeatedly until the contents were exhausted.

EXAMPLE 2

Hemostasis in Vascular Organs (Excised Cat Spleen)

Six cats of average weight of 3.5 kilograms were anesthetized intravenously with pentobarbital-sodium and prepared for aseptic surgery. Prior to surgery 25 milligrams of heparin sodium USP was intravenously administered to each cat. The spleen was exteriorized through a ventral midline incision and a disk-shaped portion of splenic tissue 1 to 2 centimetres in diameter and 3 to 5 millimetres deep was excised. Resulting profuse hemorrhage from the wound was controlled by occluding the blood supply to the spleen with soft clamps and gauze sponging. A thin layer of adhesive-forming monomer was applied to the wound surface immediately thereafter by means of the aerosol dispensing package of this invention. The monomer was applied by a momentary actuation of the aerosol apparatus with the distal end of the extension tube being held at a distance of from 4 to 8 centimetres from the wound surface. After allowing sufficient time for polymerization of the monomer, the organ was replaced in the peritoneal cavity. The ventral midline incision was closed using conventional sutures. Post-operative antibiotics and vitamin were routinely administered. Adhesive and hemostatic properties were recorded at the time of application. Five days to eight weeks after surgery necropsies were performed and the spleens examined.

In all experiments the monomer employed was 2,2,2-trifluoroethyl α-cyanoacrylate and the propellant system was a mixture of CCl_3F and CCl_2F_2 in a ratio of 40:60. The propellant to monomer ratio was 12:1.

In all experiments the monomer polymerized rapidly and provided rapid and complete hemostasis. Occasional point bleeding or seepage was controlled by a second application. With one exception, the adhesive seal remained intact, and the cats survived the initial surgery. One cat died post-operatively from hemorrhage through the splenic wound. Since the bond was complete at the time of surgery, this failing points to the need for careful replacement of the organ into the peritoneal cavity and for allowing sufficient time for complete polymerization of the monomer prior to replacement.

Examples 1 and 2 provide illustrations of the utility of the monomer-propellant systems of the invention in experimental surgical procedures in animals. Another experimental surgical procedure is end-to-end anastomosis of the small intestine, as in the dog, for demonstration of this procedure. In such work the monomer is applied to the circumference of the intestine after the ends are joined by suturing, to serve as a seal over the operative area. Several experiments of this type have shown promise for such uses.

The monomers used for biological purposes will of course be those best tolerated by the tissues. In some instances these may be "biodegradable", meaning by this term either that they are absorbed as such or are broken down into other substances which are absorbable.

For purposes of ordinary use as adhesives, monomers of the type disclosed hereinabove are applied to the surfaces to be joined in a rather thick layer, or in two layers, and these are quickly joined before complete polymerization has occurred. For such purposes the propellant-monomer ratio can be decreased, e.g. to as low as 5:1, and the propellant chosen is then one of higher volatility. In this way thicker layers of monomer are applied so that more time is available for joining the parts to be adhered before excessive polymerization has occurred.

WHAT WE CLAIM IS:—

1. A pressurized aerosol dispensing package for adhesives comprising a chemically inert, pressure-tight container having discharge passageways with a valve, a valve actuator and delivery means for controlling the escape of the contents of the container via a discharge orifice therefor, which contains an anhydrous adhesive-forming monomer dissolved in an anhydrous propellant compatible with the monomer, an inert lubricant for facilitating the escape of the contents of the container being provided within the discharge passageways so that a film of the inert lubricant is present upon the internal surfaces of the passageways of the valve, the valve actuator and the delivery means when the actuator has been operated.

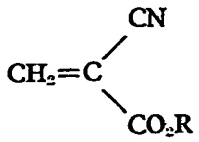
2. A pressurized aerosol dispensing package according to claim 1, in which the inert lubricant is located adjacent to and occludes the outlet of the valve and is of such density and kinematic viscosity that the vapour pressure of the anhydrous propellant, upon first being actuated, propels the inert lubricant

through the passageways of the valve actuator and the delivery means and deposits the film of lubricant thereon.

3. A pressurized aerosol dispensing package according to claim 1, in which the inert lubricant is provided upon the passageways of the valve, the valve actuator and the delivery means prior to first use of the package.

4. A pressurized aerosol dispensing package according to claim 1, 2 or 3, in which the discharge orifice is provided with means for localizing the spray discharge.

5. A pressurized aerosol dispensing package according to any preceding claim, wherein the adhesive-forming monomer comprises an alpha-cyanoacrylate ester of the formula:



wherein R is alkyl, cycloexyl, phenyl, 2(2,2,2-trifluoroethoxy)ethyl, 1,1,1-trifluoroisopropyl or CH_2R' wherein R' is a radical of the group consisting of phenyl, alkylthioalkylene, alkoxyalkylene and halogenated alkyl groups, the radical having 1 to 7 carbon atoms.

6. A pressurized aerosol dispensing package according to claim 5, wherein R is an unsubstituted alkyl group having 1 to 5 carbon atoms.

7. A pressurized aerosol dispensing package according to claim 5, wherein R is methyl.

8. A pressurized aerosol dispensing package according to claim 5, wherein R is 1,1,1-trifluoroisopropyl.

9. A pressurized aerosol dispensing package according to claim 5, wherein R is 2(2,2,2-trifluoroethoxy)ethyl.

10. A pressurized aerosol dispensing package according to claim 5, wherein R' is trifluoromethyl.

11. A pressurized aerosol dispensing package according to claim 5, wherein R' is perfluoroethyl.

12. A pressurized aerosol dispensing package according to any preceding claim, wherein the inert lubricant is a polymer wax having a density of 1 to 2.5 and a kinematic viscosity of 35 to 45 centistokes at room temperature.

13. A pressurized aerosol dispensing package according to any preceding claim, wherein the inert lubricant is poly(chlorotrifluoroethylene).

14. A pressurized aerosol dispensing package according to any preceding claim, wherein the propellant system comprises a mixture of 3 parts CCl_3F to 7 parts CCl_2F_2.

15. A pressurized aerosol dispensing package according to any of claims 1 to 13, wherein the propellant system comprises a mixture of 4 parts CCl_3F to 6 parts CCl_2F_2.

16. A pressurized aerosol dispensing package according to any of claims 1 to 13, wherein the propellant system comprises a mixture of 1 part CCl_3F to 1 part CCl_2F_2.

17. A pressurized aerosol dispensing package according to claim 5 or any of claims 6 to 16 as dependent thereon, wherein the ratio of anhydrous propellant to monomeric alpha-cyanoacrylate adhesive is in the range from 10:1 to 15:1.

18. A pressurized aerosol dispensing package according to claim 5 or any of claims 6 to 16 as dependent thereon, wherein the ratio of anhydrous propellant to monomeric alpha-cyanoacrylate adhesive is in the range from 5:1 to 20:1.

19. A pressurized aerosol dispensing package according to claim 5 or any of claims 6 to 16 as dependent thereon, wherein the ratio of anhydrous propellant to monomeric alpha-cyanoacrylate adhesive is 10:1.

20. A pressurized aerosol dispensing package according to claim 5 or any of claims 6 to 16 as dependent thereon, wherein the ratio of anhydrous propellant to monomeric alpha-cyanoacrylate adhesive is 12:1.

21. A pressurized aerosol dispensing package according to claim 1, substantially as hereinbefore described.

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1227872 COMPLETE SPECIFICATION

1 SHEET *This drawing is a reproduction of the Original on a reduced scale*

FIG. 1

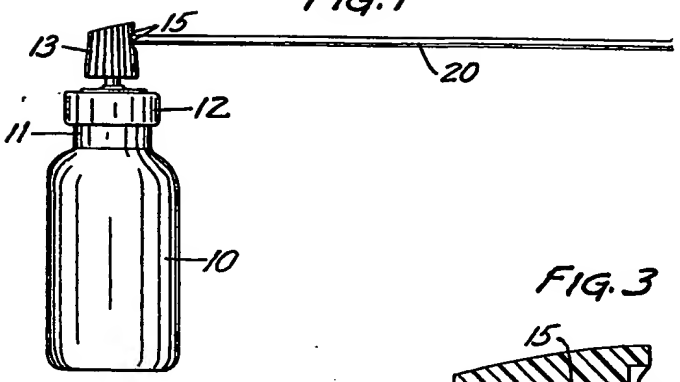

FIG. 2

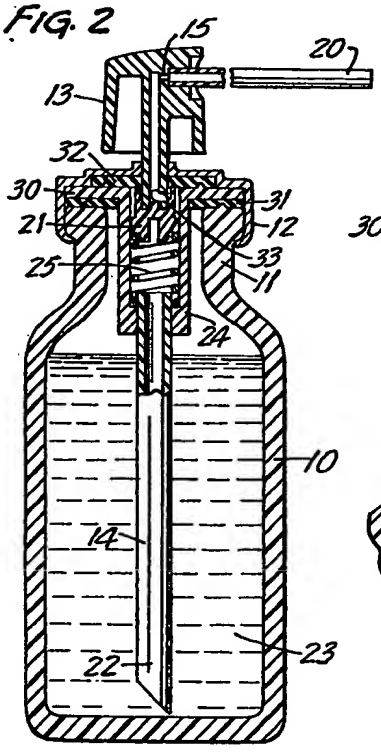

FIG. 3